PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HP/6243448	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/GB2004/003365	International filing date *(day/month/year)* 04.08.2004	Priority date *(day/month/year)* 04.08.2003

International Patent Classification (IPC) or national classification and IPC
A01N1/02, A61K31/416, A61K31/69, A61K45/06, A61P7/04, A61P9/04, A61P9/10, A61P9/12, A61P11/00, A61P29/00, A61P31/00, A61P35/00, A61P41/00

Applicant
NORTHWICK PARK INSTITUTE FOR MEDICAL RESEARCH

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.06.2005	11.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albrecht, S Telephone No. +49 89 2399-7864

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003365

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-30	as originally filed
Claims, Numbers	
1-57	received on 07.06.2005 with letter of 06.06.2005
Drawings, Sheets	
1/11-11/11	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 58,59
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-34,45-52

because:

☒ the said international application, or the said claims Nos. 18-34,45-52 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-34,46-48,50-52 (all in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-16,22-33,35-57
	No:	Claims	1-4,17-21,34
Inventive step (IS)	Yes:	Claims	5-12,22-29,36,41,54
	No:	Claims	1-4,13-21,30-35,37-40,42-53,55-57
Industrial applicability (IA)	Yes:	Claims	1-17,35-44,53-57
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Claims 18-34, 45-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.2. The attention of the applicant is drawn to the fact that for the present application only an incomplete search has been carried out with respect to claims 1-34, 46-48, 50-52, the reasons being as follows:
Claims 1-34, 46-48, 50-52 are directed to a method of treatment, as they encompass the administration of active agents to patients. However, the intended purpose is partially defined by reference to a desirable characteristic or property, namely "for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO". Such is not a method of therapy according to R.67.1(iv) PCT as the intended disease(s), disorder(s) or dysfunction(s) to be treated is/are not defined. Claims 1-36, 48-50, 52-54 cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for a limited number of such methods. Accordingly, since a meaningful search over the whole of the claimed scope is impossible, the search has thus been restricted to the diseases explicitly listed in claims 1-3, 19-21, 48-51. With respect to examination, the feature "for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent" will not be taken into consideration for the assessment of novelty and inventive step of claims 1-34, 46-48, 50-52 in view of the fact that it fails to comply with the requirements of Article 6 PCT as mentioned above.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D1-D8) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR). The cited passage(s) for each citation will

be considered unless otherwise specified.

V.1. Novelty (claims 1-34, 46-48, 50-52 under the proviso of item III.2)

V.1.1. Claims 1-4, 17-21, 34 do not appear to be novel in the sense of Article 33 (2) PCT, the reasons being as follows:

a) D3 describes the use of boranocarbonates (see examples 18-22) for treating arteriosclerosis.

Therefore, D3 is prejudicial to the novelty of claims 1, 3, 4, 17, 18, 20, 21, 34.

b) D4 pertains to N-boronated purine and pyrimidine bases, nucleoside(s) and oligonucleotide(s) for the treatment of tumours.

Hence, D4 takes away the novelty of claims 1-4, 17-21, 34.

d) D7 reports on the protective effect of a boranocarbonate (compound 2) against septic shock (table III).

Thus, D7 anticipates the subject-matter of claims 1, 3, 4, 17, 18, 20, 21, 34.

V.1.2. Claims 5-16, 22-33, 35-57 appear to be novel over the available prior art.

V.2. Inventive step (claims 1-34, 46-48, 50-52 under the proviso of item III.2)

V.2.1. Claims 1-4, 17-21, 34:

Being not new, the subject-matter of present claims 1-4, 17-21, 34 cannot be considered as inventive either.

V.2.2. Claims 13-16, 30-33, 35, 37-40, 42-53, 55-57:

a) D5, which is considered to represent the most relevant state of the art, discloses the use of metal carbonyl compounds for the therapeutic delivery of carbon monoxide (CO) as well as for organ perfusion.

b) The subject-matter of claims 13-16, 30-33, 35, 37-40, 42-53, 55-57 differs mainly from D5 in that the in D5 mentioned metal carbonyl compounds do not comprise a boron atom.

c) The technical problem to be solved by the present invention consists of providing further compositions which deliver CO to a physiological target in order to treat those diseases which respond to CO in a human/animal body (p.10) or to provide adequate perfusion of an isolated organ.

d) The solution proposed by the applicant constitutes a composition comprising a boranocarbonate.

e) Nevertheless, there is no indication supporting the fact that the technical problem can indeed be solved over the full scope of the invention, because claims 13-16, 30-33, 35, 37-40, 42-53, 55-57 do not specify that the boron atom of the claimed boranocarbonates must be adjacent to the carbonyl moiety. This is however a prerequisite for the release of CO by the claimed boranocarbonates.

Consequently, an inventive step cannot be acknowledged for present claims 13-16, 30-33, 35, 37-40, 42-53, 55-57.

V.2.3. Claims 5-12, 22-29, 36, 41, 54:

a) D5 is considered to represent the most relevant state of the art.

b) The subject-matter of claims 5-12, 22-29, 36, 41, 54 differs from D5 in that the in D5 mentioned metal carbonyl compounds do not comprise a boron atom.

c) The technical problem to be solved by the present invention consists of providing further compositions which deliver CO to a physiological target in order to treat those diseases which respond to CO in a human/animal body (p.10) or to provide adequate perfusion of an isolated organ.

d) The solution proposed by the applicant constitutes a composition comprising a boranocarbonate as defined in claims 5-12.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

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e) D6 describes the use of boranocarbonates as CO source and as reducing agent in the chemical synthesis of transition metal carbonyl complexes. In particular, the CO is released upon heating an aqueous solution of the boranocarbonate (cf. p.2, l.34-35 and examples 2,3 in which the solution is heated to 75°C). Furthermore, it is specified in this document that the boranocarbonates may also be applied in other circumstances wherein a CO source in aqueous solution is required (p.7, l.10-14). Nevertheless, D6 does not contain any indication that boranocarbonates are able to release CO under physiological conditions. In addition, the applicant has provided evidence that the technical problem can be solved by the present invention.

f) Hence, claims 5-12, 22-29, 36, 41, 54 appear to involve an inventive step in the sense of Art.33(3) PCT.

V.3. Industrial Applicability

For the assessment of the present claims 18-34, 45-52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03066067	14/08/2003	03/02/2003	04/02/2002